

FIGURE 1

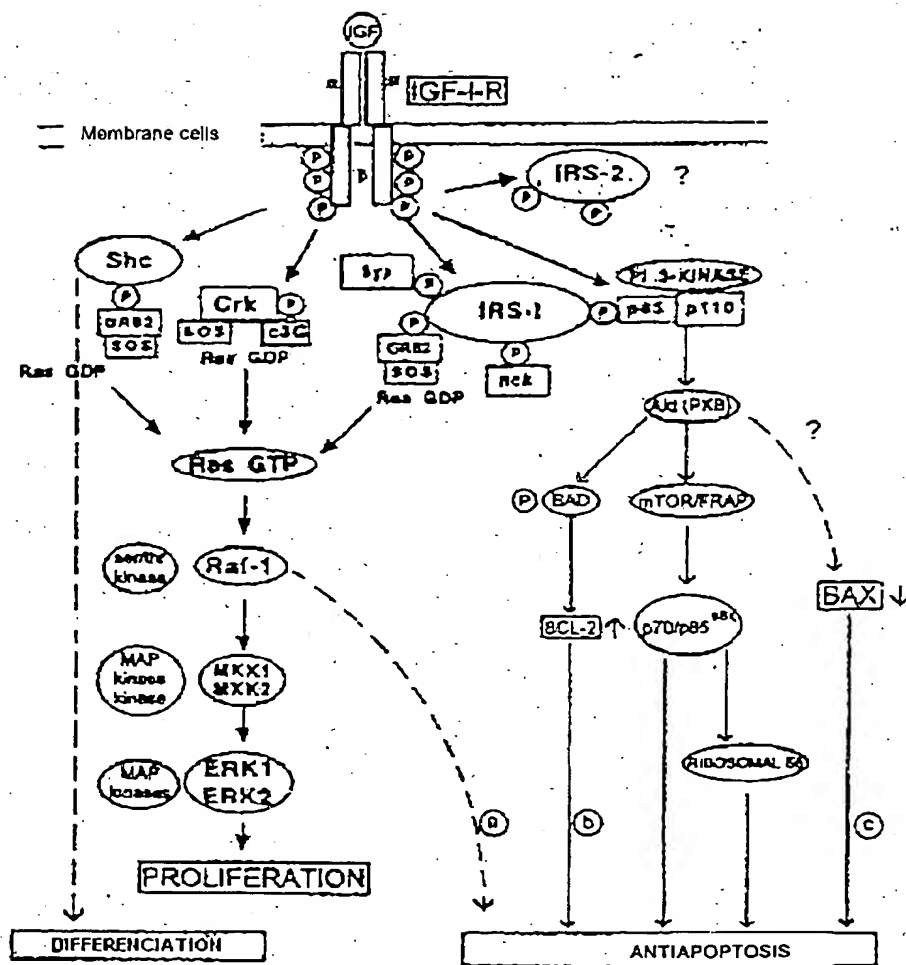


FIGURE 2

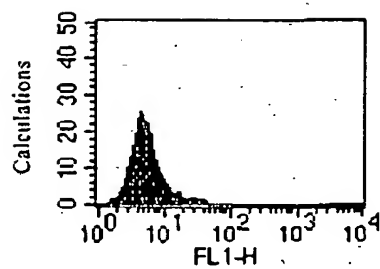


FIGURE 3A

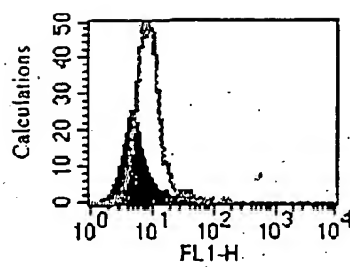


FIGURE 3B

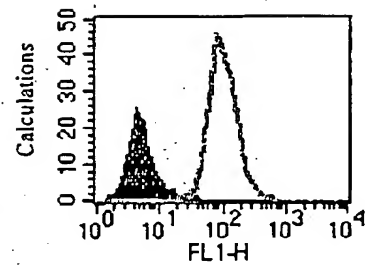
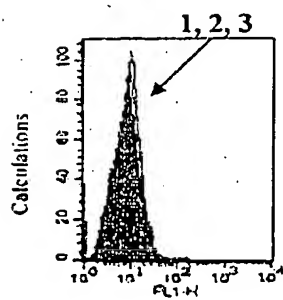
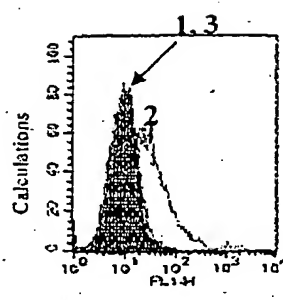


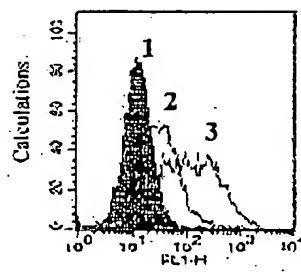
FIGURE 3C



Nontransfected cells



IGF-IR+ cells



IR+ cells

FIGURE 4A

FIGURE 4B

FIGURE 4C

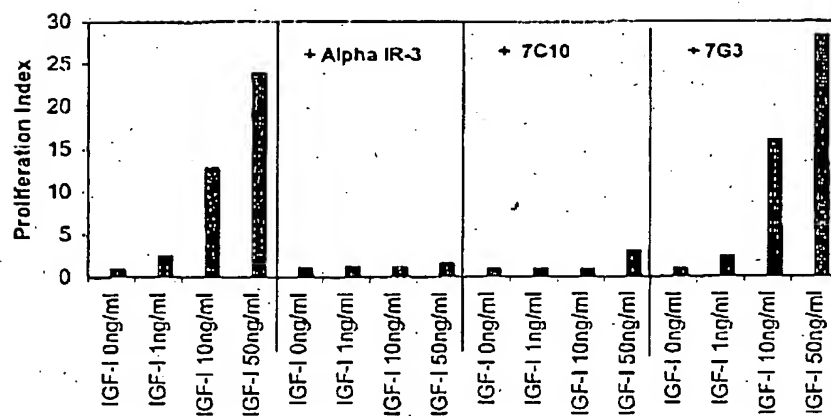


FIGURE 5

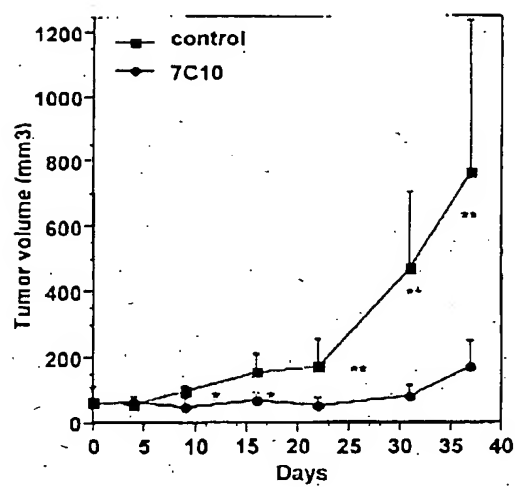


FIGURE 6A

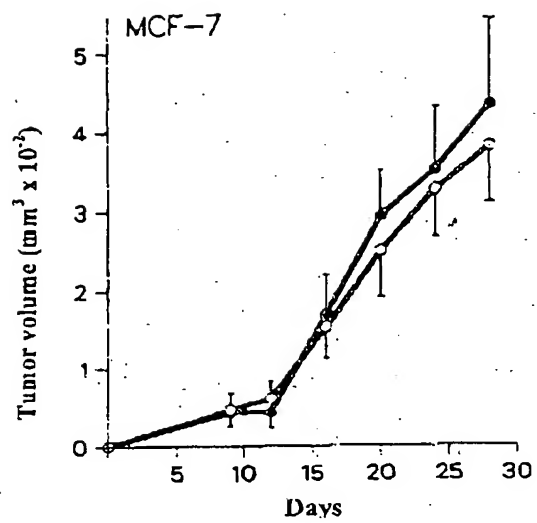


FIGURE 6B

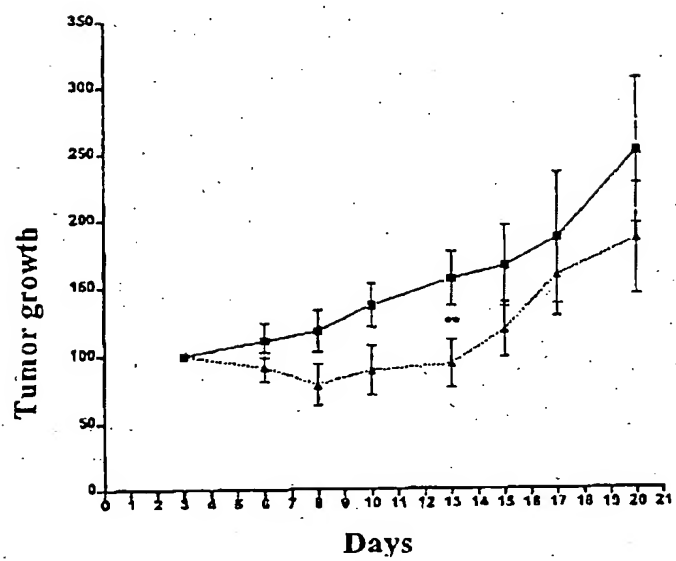


FIGURE 6C

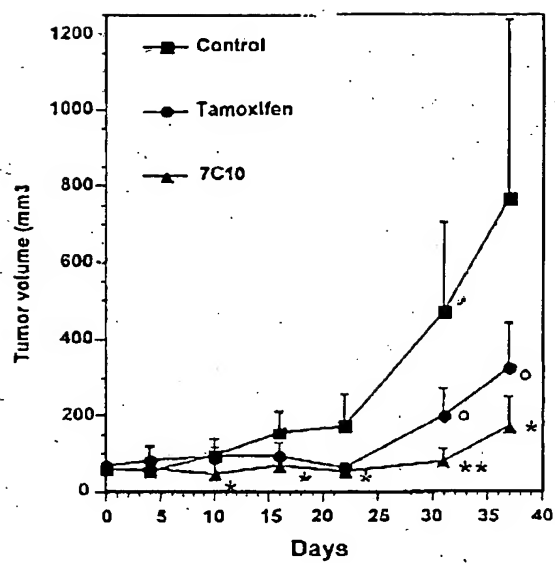


FIGURE 7

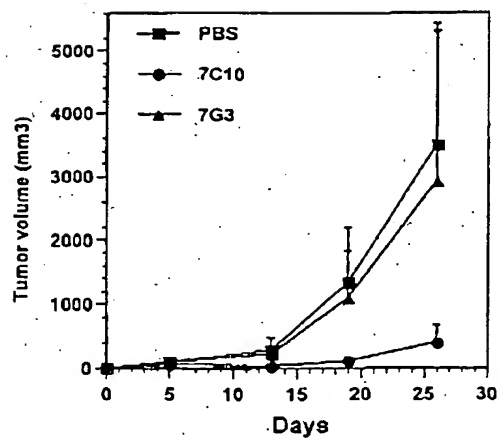


FIGURE 8A

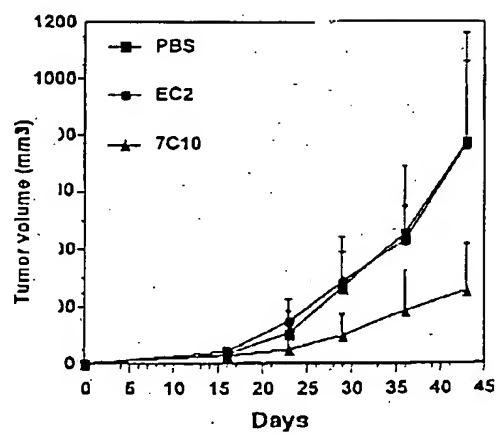


FIGURE 8B

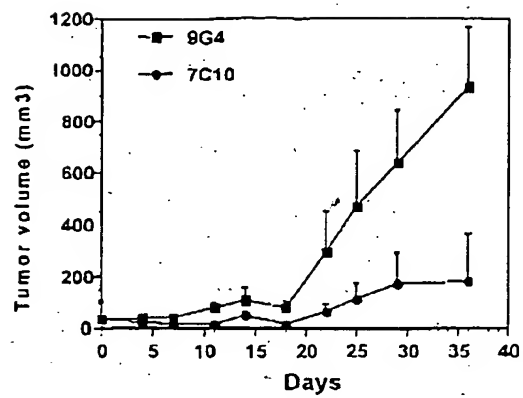


FIGURE 8C

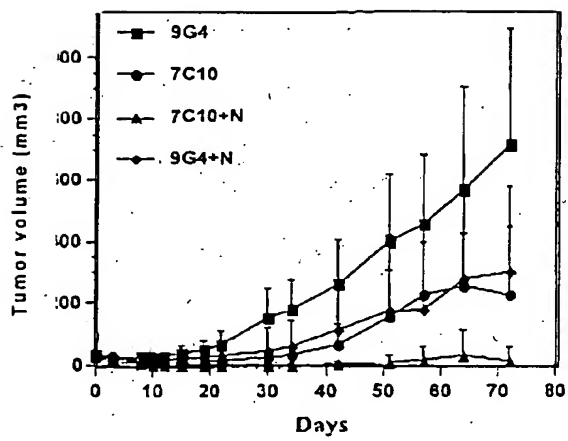


FIGURE 9

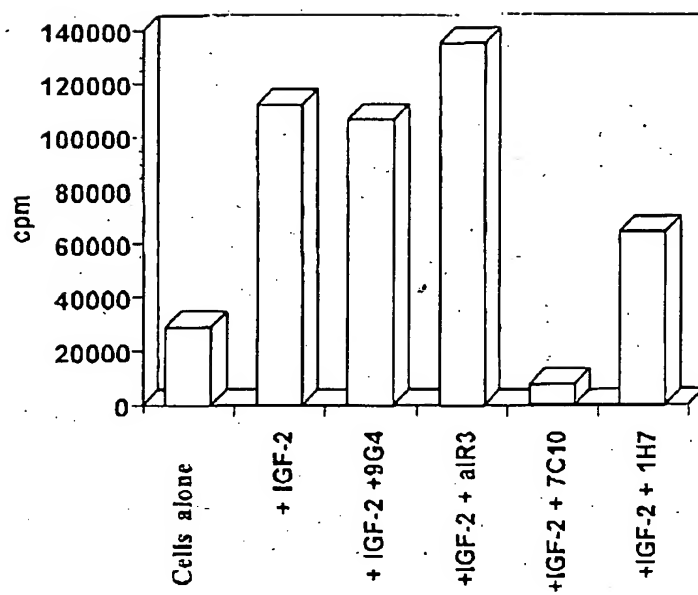


FIGURE 10

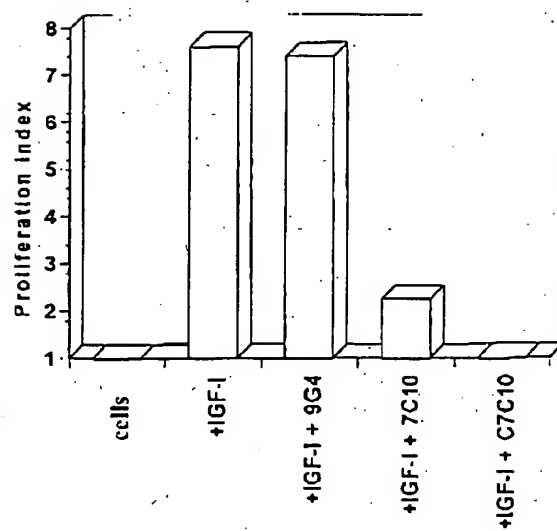


FIGURE 11



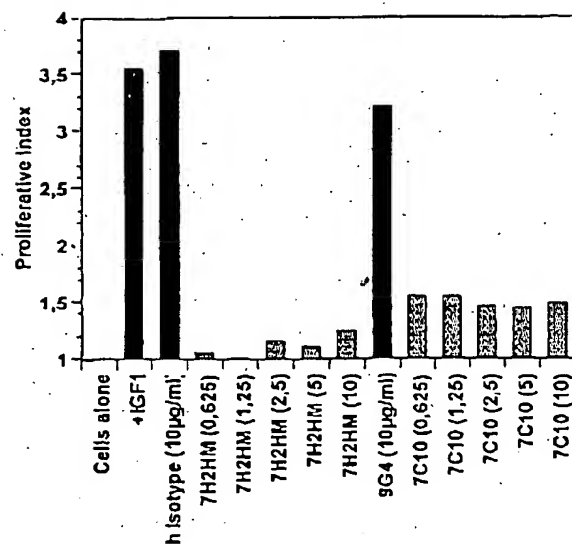


FIGURE 12

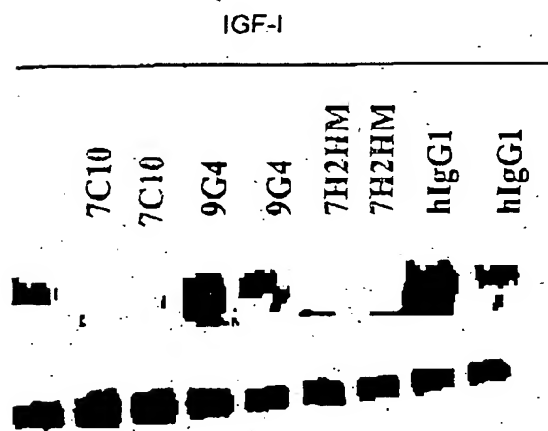


FIGURE 13

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1 ATGAAGTTGCCTGTTAGCCTGTTGGTGCTGATGTTCTGGATTCTGCTTCCAGAAGTGAT
-----+-----+-----+-----+-----+ 60
TACTTCAACGGACAATCCGACAACCACCACTACAAGACCTAAGGACGAAGGTCTTCACTA
ATGAAGTTGCCTGTTAGGCTGTTGGTGCT
oligo MKV-1      L M F W I P A S R S D
                  3' end      leader peptide
61 GTTTTGATGACCCAAATTCCACTCTCCCTGCCTCTCAGTCTTGGAGATCAAGCCTCCATC
-----+-----+-----+-----+-----+ 120
CAAACTACTGGGTTTAAGGTGAGAGGGACGGACAGTCAGAACCCTCTAGTTCGGAGGTAG

V L M T Q I P L S L P V S L G D O A S I -
121 TCTTCAGATCTAGTCAGAGCATTGTACATAGTAATGGAACACCTATTTACAATGGTAC
-----+-----+-----+-----+-----+ 180
AGAACGTCTAGATCACTCTCGTAACATGTATCATTACCTTTGTGGATAAATGTTACCATG

S C R S S O S I V H S N G N T Y L Q W Y -
CDR 1
181 CTGCAGAAACCAGGTCAGTCTCCAAAGCTCTGATCTACAAAGTTTCCAACCGACTTTAT
-----+-----+-----+-----+-----+ 240
GACGTCTTTGGTCCAGTCAGAGGTTTCGAGGACTAGATCTTTCAAAGGTTGGCTGAAATA

L Q K P G Q S P K L L I Y K V S N R L Y -
CDR 2
241 GGGGTCACAGACAGGTTCAAGTGGCAGTGGATCAGGGACAGATTTCACACTCAAGATCAGC
-----+-----+-----+-----+-----+ 300
CCCCAGGGTCTGTCCAAGTCACCGTCACCTAGTCCCTGTCTAAAGTGTGAGTTCAGTCG

G V P D R F S G S G S G T D F T L K I S -
301 AGCGTGGAGGCTGAGGATCTGCCAGTTTATTACTGCTTTCAAGGTTTCAATGTTCGGTGG
-----+-----+-----+-----+-----+ 360
TCGCACCTCCCACTCCTAGACCCTCAAATAATGACGAAGTTCCAAGTGTACAAGGCACC

S V E A E D L G V Y Y C F Q G S H V P W -
CDR 3
361 ACGTTCGGTGGAGGCACCAAGCTGGAATCAAACGGGCTGATGCTGCACCAACTGTATCC
-----+-----+-----+-----+-----+ 420
TGCAAGCCACCTCCGTGGTTTCGACCTTTAGTTTGCCCGACTACGACGTGGTTGACATAGG

I F G G G T K L E I K
MKC oligo
TAGAAGGGTGGTAGGTCA
ATCTTCCCACCATCCAGT
421 -----+-----+-----+-----+ 438
TAGAAGGGTGGTAGGTCA

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FIGURE 14

1 ATGATGGTCTTAAGTCTTCTGTACCTCTTGACAGCCATTCTGGTATCCTGTCTGTATGTA 60  
 TACTACCACAAATTCAGAAGACATGGACAACCTGTCGGTAAGGACCATAGGACAGACTACAT  
 MHV-12 ATGATGGTGTAAAGTCTTCTGTACCT  
 MHV-8 ATGAGAGTGCTGATTCTTTTGTG

L L T A I P G I L S D V -  
 3' end leader peptide

61 CAGCTTCAGGAGTCAGGACCTGGCCTCGTGAACCTTCTCAGTCTCTGTCTCTCACCTGC 120  
 GTCGAAGTCCTCAGTCTCGGACCGGAGCACTTTGGAAGAGTCAGAGACAGAGAGTGGACG  
 Q L Q E S G P G L V K P S O S L S L T C -  
 TCTGTACCGGGCTACTCCATCACCGGTGGTTATTTATGGAACCTGGATCCGGCAGTTTCCA  
 121 AGACAGTGGCCGATCACCTAGTGGCCACCAATAAATACCTTGACCTAGGCCGTCAAAGGT 180  
 S V T G Y S I T G G Y L W N W I R Q F F -  
 CDR 1  
 CGAAACAACTGGAGTGCATGGGCTACATAAGCTACGACGGTACCAATAACTACAAACCA  
 181 CCTTTGTTGACCTCACCTACCCGATGTATTCCATGCTGCCATGGTTATTGATGTTTGGT 240  
 G N K L E W M G Y I S Y D G T N N Y K P -  
 CDR 2  
 TCTCTCAAAGATCGAATCTCCATCACTCGTGACACATCTAAGAACCAGTTTTCTCTGAAG  
 241 AGACAGTTTCTAGCTTAGAGGTACTGAGCACTGTGTAGATTCTTGGTCAAAAAGGACTTC 300  
 S L K D R I S I T R D T S K N Q F F L K -  
 TTCAATCTGTGACTAATGAAGACACAGCTACATATTACTGTGCAAGATACGGTAGGGTC  
 301 AACTTAAGACACTGATTACTTCTGTGTGATCTATAATGACACGTTCTATCCCATCCAG 360  
 I N S V T N E D T A T Y Y C A R Y G R V -  
 CDR 3  
 GGG  
 TTCTTTGACTACTGGGGCCAAGGCACCACTCTCACAGTCTCCTCAGUCAAACGACACCC  
 361 AAGAACTGATGACCCCGGTTCCGTGGTGAGAGTETCAGAGGAGTCGGCTTTTGCTGTGGG 420  
 F F D Y W G Q G T T L T V S S  
 oligo MHC-1  
 GGTAGACAGATAGGTGAC  
 CCATCTGTCTATCCACTG  
 421 GGTAGACACATAGGTGAC 438

FIGURE 15

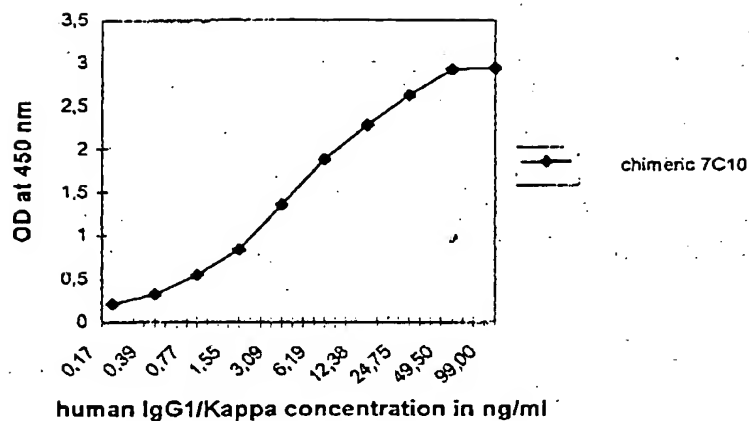


FIGURE 16

	3	7		CDR 1
7C10 VL mouse	D	V	L	M
DRB1-4.3		T		
C94-5B11' CL		T		
Kabat sgII mouse	V	T		

				CDR 2
7C10 VL mouse	W	Y	L	Q
DRB1-4.3				
C94-5B11' CL				
Kabat sgII mouse				

	77			CDR 3
7C10 VL mouse	K	I	S	S
DRB1-4.3	R			
C94-5B11' CL	R			
Kabat sgII mouse	R			

FIGURE 17

CDR 1

7C10 VL mouse	DVLMTQIPLSLPVSLGDQASISC	<u>RSSQSIVHSNGNTYLO</u>
GM607	.IV...S.....TP.EP.....	.....LL....YN..D
DPK15/A19	.IV...S.....TP.EP.....	.....LL....YN..D
Kabat sgII hu	.IV...S.....TP.EP.....	.....LL..D.XX..X

CDR 2

7C10 VL mouse	WYLQKPGQSPKLLIY	<u>KVSNRLY</u>	GVPDRFSGSGSGTDFTLK
GM607	.....Q.....	LG...AS	.....
DPK15/A19	.....Q.....	LG...AS	.....
Kabat sgII hu	.....Q.....	L...AS	.....

CDR 3

7C10 VL mouse	ISSVEAEDLGVYYC	<u>FOGSHVPWT</u>	FGGGTKLEIK
GM607	..R.....V.....	M.ALQT.Q.	..Q...V...
DPK15/A19	..R.....V.....	M.ALQT.	
Kabat sgII hu	..R.....V.....	M.ALQX.R.	..Q...V...

FIGURE 18

CDR 1

7C10 VL mouse	DVLMTQIPLSLPVSLGDQASISC	<u>RSSQSIVHSNGNTYLO</u>
GM 607	.IV...S.....TP.EP.....	.....LL....YN..D
7C10 VL Humanized 1	..V...S.....TP.EP.....	.....
7C10 VL Humanized 2	.IV...S.....TP.EP.....	.....

CDR 2

7C10 VL mouse	WYLQKPGQSPKLLIY	<u>KVSNRLY</u>	GVPDRFSGSGSGTDFTL
GM 607	.....Q.....	LG...AS	.....
7C10 VL Humanized 1	.....Q.....		
7C10 VL Humanized 2	.....Q.....		

CDR 3

7C10 VL mouse	KISSVEAEDLGVYYC	<u>FOGSHVPWT</u>	FGGGTKLEIK
GM 607	..R.....V.....	M.ALQT.Q.	..Q...V...
7C10 VL Humanized 1	..R.....V.....		..Q...V...
7C10 VL Humanized 2	..R.....V.....		..Q...V...

FIGURE 19

MluI

1 GTCAGAACGCGTGCCGCCACCATGAAGTTCCTGTTAGGCTGTGGTGCTCATGTTCTGG 60  
 CAGTCTTGCGCACGCGGTGGTACTTCAACGGACAATCCGACAACCACGACTACAAGACC

M K L P V R L L V L M F W -  
 Peptide leader

61 TTTCTGCTTCCAGCAGTGATGTTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCACC 120  
 AAAGGACGAAGGTGCTCACTACAACACTACTGAGTCAGAGGTGAGAGGGACGGGCAGTGG  
 F P A S S S D V V M T Q S P L S L P V T -

121 CCTGGAGAGCCGGCCTCCATCTCCTGCAGGTCTAGTCAGAGCATTGTACATAGTAATGGA 180  
 GGACCTCTCGGCCGGAGGTAGAGGACGTCCACATCAGTCTCGTAACATGTATCATTACCT  
 CDR 1  
 P G E P A S I S C R S S Q S I V H S N G -  
 KpnI

181 AACACCTATTTGCAATCGTACCTGCAGAAGCCAGGGCAGTCTCCACAGCTCCTGATCTAT 240  
 TTGTGGATAAACGTTACCATGGACGTCTTCGGTCCCGTCAGAGGTGTCGACCACTACATA  
 N T Y L Q W Y L Q K P G Q S P O L L I Y -

241 AAAGTTTCTAATCGGCTTTATGGGGTCCCTGACAGGTTCAAGTGGCAGTGCATCAGGCACA 300  
 TTTCAAAGATTAGCCGAAATACCCCGAGGACTGTCCAAGTCACCGTCACCTAGTCCCTGT  
 CDR 2  
 K V S N R L Y G V P D R F S G S Q S G T -

301 GATTTTACACTGAAATCAGCAGAGTGGAGGCTGAGGATGTGGGGTTTATTACTGCTTT 360  
 CTAAAATCTGACTTTTAGTCTGCTCACCTCCGACTCCTACAACCCCAAATAATGACGAAA  
 D F T L K I S R V E A E D V G V Y Y C F -

361 CAAGGTTACATGTTCCGTGGACGTTCCGGCCAAGGGACCAAGGTGGAAATCAAACGTGAG 420  
 GTTCCAAGTGTAAGGCACCTGCAAGCCGGTTCCCTGGTTCCACCTTTAGTTTGCACTC  
 CDR 3  
 O G S H V P W T F G Q G T K V E I K  
 BamHI

421 TGGATCCTCTGCG 433  
 ACCTAGGAGACGC

FIGURE 20



	17	27	CDR 1
7C10 VH	DVQLQESGPGLVKPSQSLTCSVTGYSIT	GGYLWN	WIRQ
AN03' CL	.....	S..Y..	.....
Kabat sgI(A)	E.....S.....T.....D.....	S..WN.	.....

	CDR 2
7C10 VH	FPGNKLEWMG YISYDGTNNYKPSLKD RISITRDTSKNQFFL
AN03' CL	.....N...N...N...N.....
Kabat sgI(A)	.....S.STY.N.....S.....Y..

	84	CDR 3
7C10 VH	KLNSVTNEDTATYYCAR	YGRV-FFDY WGQGTTLTVSS
AN03' CL	.....T.....	E.YGY.....
Kabat sgI(A)	Q.....T.....	G.YGYG.....V.....

FIGURE 22

	Rch 1	30	CDR 1	Rch 2
7C10 VH mouse	DVQLQESGPGLVKPSQSLTCSVTGYSIT	GGYLWN	WIRQ	
human Kabat sgII	Q.....T.....T.S.G.VS	SYWS..	.....	
human VH FUR1'CL	Q.....ET.....T.S.....S	S..Y.S	.....	
human Germline	Q.....ET.....T.S.....S	S..Y.S	.....	
	Rch 2	49	CDR 2	67 71 Rch 3
7C10 VH mouse	FPGNKLEWMG YISYDGTNNYKPSLKD	RISITRDTSKNQFFL		
human Kabat sgII	P..KG...I. R.Y.S.STX.N....S	.VT.SV.....S.		
human VH FUR1'CL	P..KG...I. SMFHS.SSY.N....S	.VT.SV.....S.		
human Germline	P..KG...I. S.YHS.STY.N....S	.VT.SV.....S.		
	Rch 3		CDR 3	Rch 4
7C10 VH mouse	KLNSVTNEDTATYYCAR	YGRVFFDY	WGQGTTLTVSS	
human Kabat sgII	..S...AA...V.....	ELPGGYDV	.....LV....	
human VH FUR1'CL	Q.R...AA...V.....	GRYCSSTSCNWEDP	.....LV....	
human Germline	..S...AA...V.....			

FIGURE 23



		30	CDR 1	48
7C10 VH mouse	DVQLQESGPGGLVKPSQSLTCSVTGYSIT	<u>GGYLWN</u>	WIRQFPGNKLEWMG	
human germline	Q.....ET.....T.S..... <u>S</u>	S..Y.G	....P..KG... <u>I</u> .	
VH Humanized 1	Q.....ET.....T.S.....		....P..KG.....	
VH Humanized 2	Q.....ET.....T.S.....		....P..KG... <u>I</u> .	
VH Humanized 3	Q.....ET.....T.S..... <u>S</u>		....P..KG... <u>I</u> .	

	CDR 2	67	71
7C10 VH mouse	<u>YISYDGTNNYKPSLKD</u>	RISITR	DTSKNQFFLKLNSVTNEDTATYYCAR
human germline	S.FHS.SSY.N....S	<u>VT</u> . <u>SV</u> .....S...S...AA...V.....	
VH Humanized 1	.....	T.S.....S...S...AA...V.....	
VH Humanized 2	.....	<u>VT</u> .S.....S...S...AA...V.....	
VH Humanized 3	.....	<u>VT</u> . <u>SV</u> .....S...S...AA...V.....	

	CDR 3
7C10 VH mouse	<u>YGRVFFDY</u> WGQGTTLTVSS
human germline	
VH Humanized 1	.....LV.....
VH Humanized 2	.....LV.....
VH Humanized 3	.....LV.....

FIGURE 24

MluI

```

      |
GTCAGAACGCGTGCCGCCACCATGAAAGTGTTGAGTCTGTTGTACCTCTTGACACCCATT
1  -----+-----+-----+-----+-----+ 60
CAGTCTTGCGCACGGCGGTGGTACTTTCACAACCTCAGACAACATGGAGAAGTGTCTGGTAA

      M K V L S L L Y L L T A I -
      Leader peptide
CCTGGTATCCTGTCTCAGGTGCAGCTTCAGGAGTCGGGGCCAGGACTGGTGAAGCCTTCG
61 -----+-----+-----+-----+-----+ 120
GGACCATAGGACAGAGTCCACGTGGAAGTCTCAGCCCGGGTCTGACCACTTCGGAAGC

      P G I L S Q V Q L Q E S G P G L V K P S -
GAGACCCTGTCCCTCACCTGCACTGTCTCTGGTACTCCATCACCGCTCGTTATTTATGG
121 -----+-----+-----+-----+-----+ 180
CTCTGGGACAGGGAGTGGACGTGACAGAGACCAATGAGGTAGTGGCCACCAATAAATACC
      30 CDR 1
E T L S L T C T V S G Y S T T G G Y L W -
AACTGGATACGGCAGCCCCCAGGGAGGGACTGGAGTCGATGGGGTATATCAGCTACGAC
181 -----+-----+-----+-----+-----+ 240
TTGACCTATGCCGTGGGGGTCCCTTCCTGACCTCAGCTACCCCATATAGTCGATGCTG
      48
N W I R Q P P G K G L E W M G Y I S Y D -
      KpnI
      |
GGTACCAATAACTACAAACCCTCCCTCAAGGATCGAATCACCATATCAGGTGACACGTCC
241 -----+-----+-----+-----+-----+ 300
CCATGGTTATTGATGTTTGGGAGGCAGTTCCTAGCTTAGTGGTATAGTGCAGTGTGCAGG
      CDR 2 67 71
G T N N Y K P S L K D R I T I S R D T S -
AAGAACCAGTTCTCCCTGAAGCTGAGCTCTGTGACCGCTGCGGACACTGCAGTGTATTAC
301 -----+-----+-----+-----+-----+ 360
TTCTTGGTCAAGAGGGACTTCGACTCGAGACACTGGCGACGCTGTGACGTCACATAATG

K N Q F S L K L S S V T A A D T A V Y Y -
TGTGCGAGATACGGTAGGGTCTTCTTTGACTACTGGGGCCAGGGAACCCCTGGTCACCGTC
361 -----+-----+-----+-----+-----+ 420
ACACGCTCTATGCCATCCCAGAAGAACTGATGACCCCGGTCCCTTGGGACCACTGGCAG
      CDR 3
C A R Y G R V F F D Y W G Q G T L V T V -

      BamHI
      |
TCCTCAGGTGAGTGCATCCTCTGCG
421 -----+-----+-----+-----+ 445
AGGAGTCCACTCACCTAGGAGACGC

S S -

```

FIGURE 25

MluI  
 |  
 GTCAGAACGCGTGCCGCCACCATGAAAGTGTGAGTCTGTTGTACCTCTTGACAGCCATT  
 -----+-----+-----+-----+-----+ 60  
 CAGTCTTGCGCACGGCGGTGGTACTTTCACAACCTCAGACAACATGGAGAACTGTCGGTAA  
  
                   M K V L S L L Y L L T A I -  
                                   Leader peptide  
 CCTGGTATCCTGTCTCAGGTGCAGCTTCAGGAGTCGGGCCAGGACTGGTGAAGCCTTCG  
 -----+-----+-----+-----+-----+ 120  
 61 GCAGCATACCACAGAGTCCACGTCGAAGTCTCAGCCCGGGTCTGACCACTTCGGAAGC  
  
 P G I L S Q V Q L Q E S G P G L V K P S -  
 GAGACCCTGTCCCTCACCTGCACTGTCTCTGGTTACTCCATCACCGGTGGTTATTTATCG  
 -----+-----+-----+-----+-----+ 180  
 121 CTCTGGGACAGGAGTGGACGTGACAGAGACCAATGAGCTAGTCGCCACCAATAAATACC  
                                   30 CDR 1  
 E T L S L T C T V S G Y S I T G G Y L W -  
 AACTCCATACGGCAGCCCCCAGCGAAGGGACTGGAGTGGATCGGCTATATCAGCTACGAC  
 -----+-----+-----+-----+-----+ 240  
 181 TTGACCTATGCCGTCCGGGGTCCCTTCCTGACCTCAGCTAGCCCATATAGTCGATGCTG  
                                   48  
 N W I R Q P P G K G L E W I G Y I S Y D -  
  
 KpnI  
 |  
 GGTACCAATAACTACAAACCTCCCTCAAGGATCGAGTCACCATATCACGTGACACGTCC  
 -----+-----+-----+-----+-----+ 300  
 241 CCATGGTTATTGATGTTTGGGAGGGAGTTCTAGCTCAGTGGTATAGTGCACCTGTGCAGG  
                   CDR 2 67 71  
 G T N N Y K P S L K D R V T I S R D T S -  
 AAGAACCAGTCTCCCTGAAGCTGAGCTCTGTGACCGCTGCGGACACTGCAGTGTATTAC  
 -----+-----+-----+-----+-----+ 360  
 301 TTCTTGGTCAAGAGGGACTTCGACTCGAGACACTGGCGACGCTGTGACGTACATAATG  
  
 K N Q F S I K I S S V T A A D T A V Y Y -  
 TGTGCGAGATACGGTAGGGTCTTCTTTGACTACTGGGGCCAGGGAACCCCTGCTCACCGTC  
 -----+-----+-----+-----+-----+ 420  
 361 ACACGCTCTATGCCATCCCAGAAAGAACTGATGACCCCGGTCCCTTGGGACCACTGGCAG  
                   CDR 3  
 C A R Y G R V E F D Y W G O G T L V T V -  
  
 BamHI  
 |  
 TCCTCAGGTGAGTGGATCCTCTGCG  
 -----+-----+-----+-----+ 445  
 421 AGGAGTCCACTCACTAGGAGACGC  
  
 S S -

FIGURE 26

MluI  
 |  
 CTCAGAACGCGTGCCGCCACCATGAAAGTGTGAGTCTGTGTACCTCTTGACAGCCATT  
 1 -----+-----+-----+-----+-----+ 60  
 CAGTCTTGCGCACCGCGGTGGTACTTTCACTCACAACATGGAGAACTGTCGGTAA  
  
 M K V L S L L Y L L T A I -  
 Leader peptide  
 CCTGGTATCCTGTCTCAGGTGCAGCTTCAGGAGTCGGGCCAGGACTGGTGAAGCCTTCG  
 61 -----+-----+-----+-----+-----+ 120  
 GGACCATAGGACAGAGTCCACGTGGAAGTCCCTAGCCCGGGTCTGACCACTTCGGAAGC  
  
 P G I L S Q V Q L O E S G F G L V K P S -  
 GAGACCCTGTCCCTCACCTGCACTGTCTCTGGTTACTCCATCAGCGGTGGTTATTTATGG  
 121 -----+-----+-----+-----+-----+ 180  
 CTCTGGGACAGGGAGTGGACGTGACAGAGACCAATGAGGTAGTCCGCCACCAATAAATACC  
 E T L S L T C T V S G Y S I S G G Y I W -  
 AACTGGATACGGCAGCCCCCAGGCAACCGCACTGGAGTGGATCGGGTATATCAGCTACGAC  
 181 -----+-----+-----+-----+-----+ 240  
 TTGACCTATGCCGTGCGGGTCCCTTCCTGACCTCACCTACCCCATATAGTCGATGCTG  
 N W I R Q P P G K G L E W I G Y I S Y D -  
 KpnI  
 |  
 GGTACCAATACTACAAACCTCCCTCAAGGATCGAGTCACCATATCAGTGGACACGTCC  
 241 -----+-----+-----+-----+-----+ 300  
 CCATGGTTATTGATGTTTGGGAGGGAGTTCCTAGCTCAGTGGTATAGTCACCTGTGCAGG  
 C T N N Y K P S L K D R V T I S V D T S -  
 AAGAACCAGTTCTCCCTGAAGCTGAGCTCTGTGACCGCTGCGGACACTGCAGTGTATTAC  
 301 -----+-----+-----+-----+-----+ 360  
 TTCTTGGTCAAGAGGGACTTCGACTCGAGACACTGGCGACGCCTGTGACGTCACATAATG  
  
 K N Q P S L K L S S V T A A D T A V Y Y -  
 TGTGCGAGATACGGTAGGGTCTTCTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTC  
 361 -----+-----+-----+-----+-----+ 420  
 ACACGCTCTATGCCATCCCAGAAGAACTGATGACCCCGGTCCCTTGGGACCACTGGCAG  
 C A R Y G R V F F D Y W G Q G T L V T V -  
 BamHI  
 |  
 TCCTCAGGTGAGTGGATCCTCTGCG  
 421 -----+-----+-----+-----+ 445  
 AGGAGTCCACTCACCTAGGAGACGC  
  
 S S

FIGURE 27

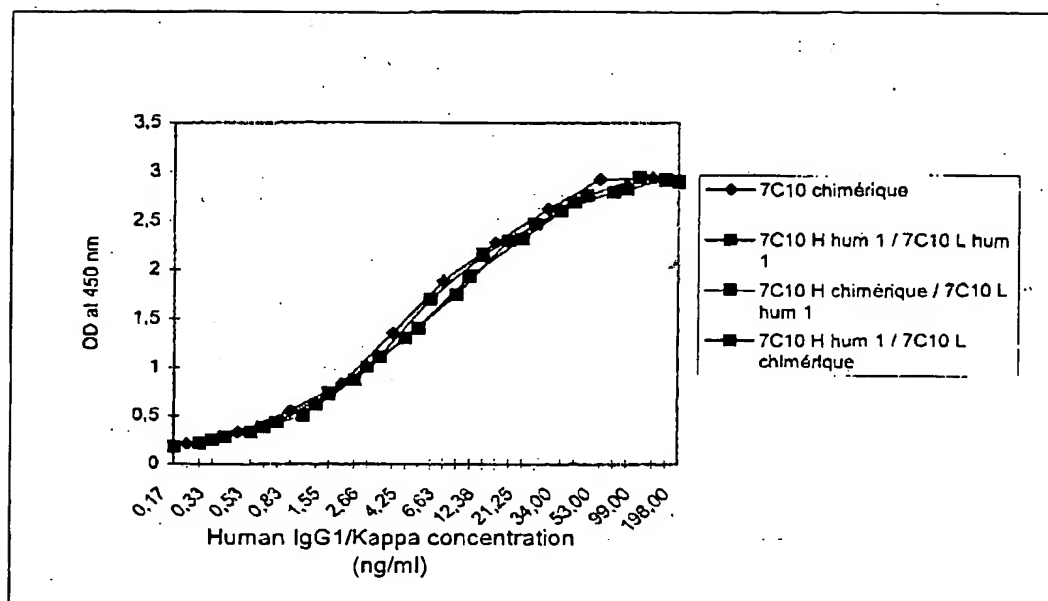


FIGURE 28

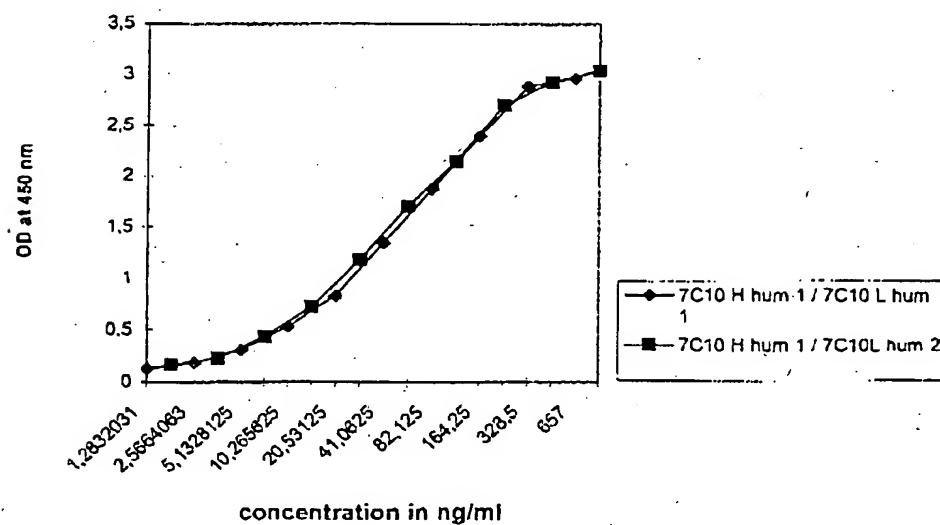


FIGURE 29

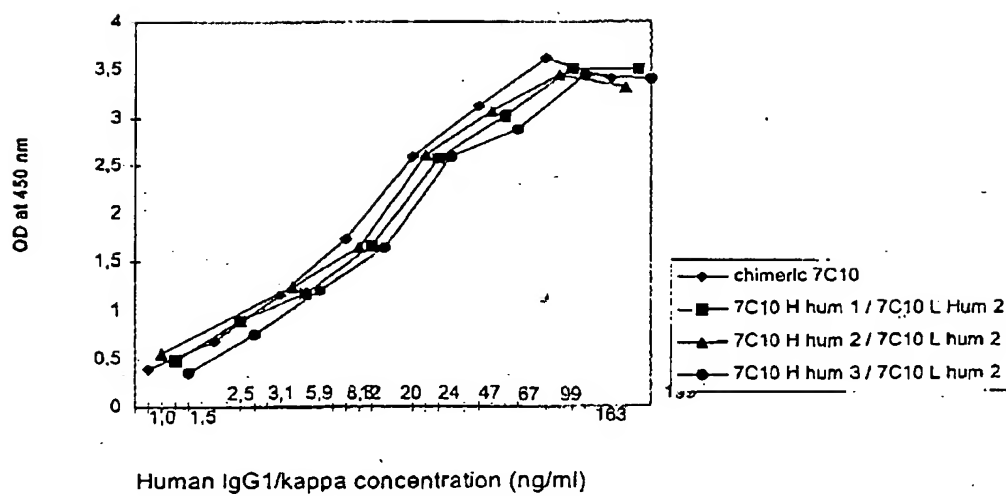
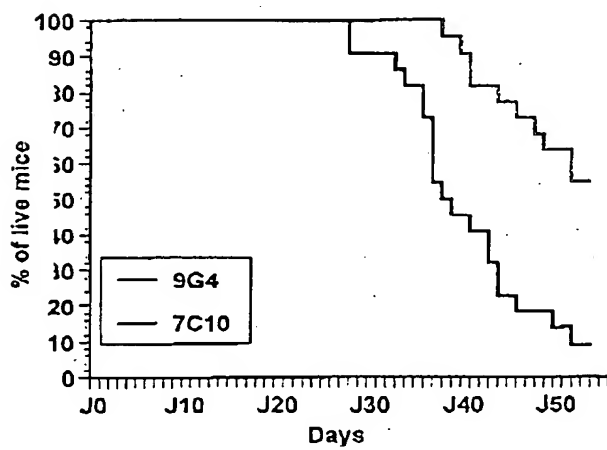
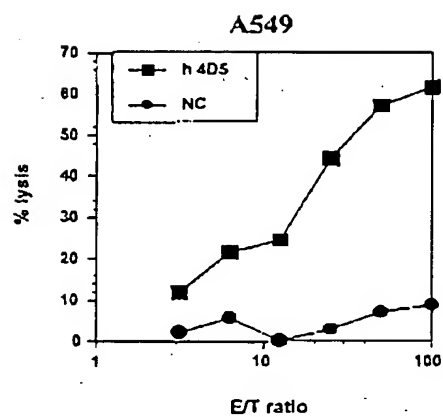
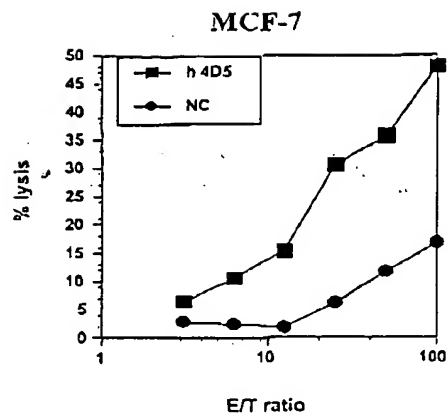


FIGURE 30

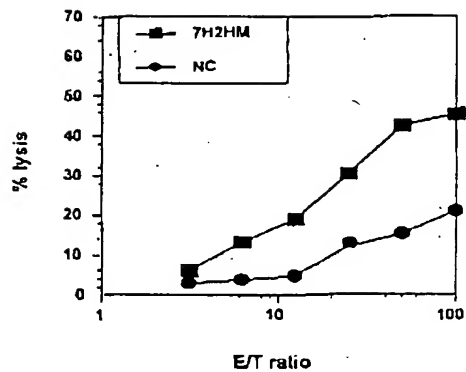




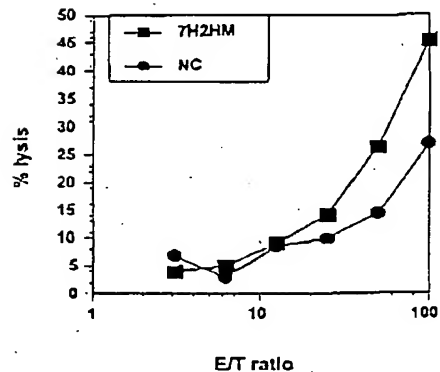
**FIGURE 32A**



**FIGURE 32B**



**FIGURE 32C**



**FIGURE 32D**

- IGF1

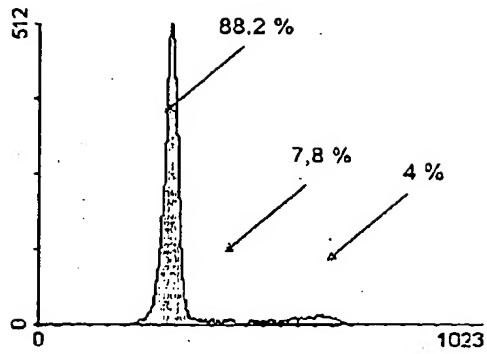


FIGURE 33A

+ IGF1 (50 ng/ml)

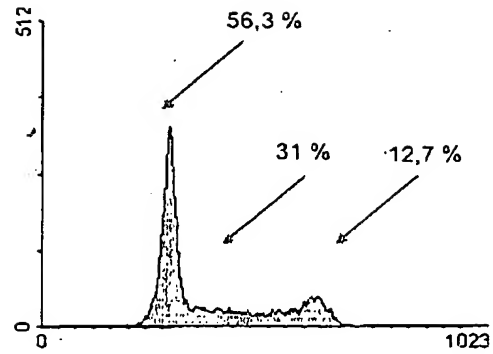


FIGURE 33B

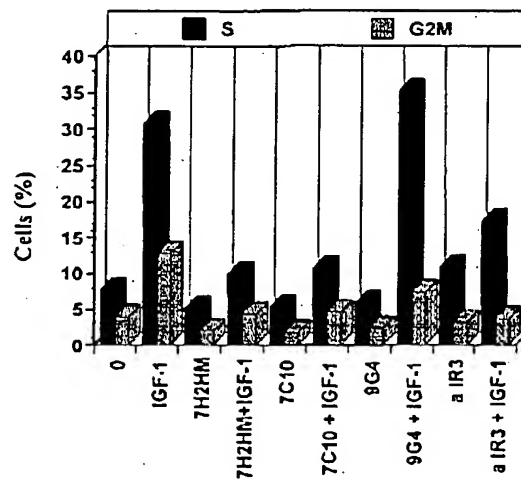


FIGURE 33C



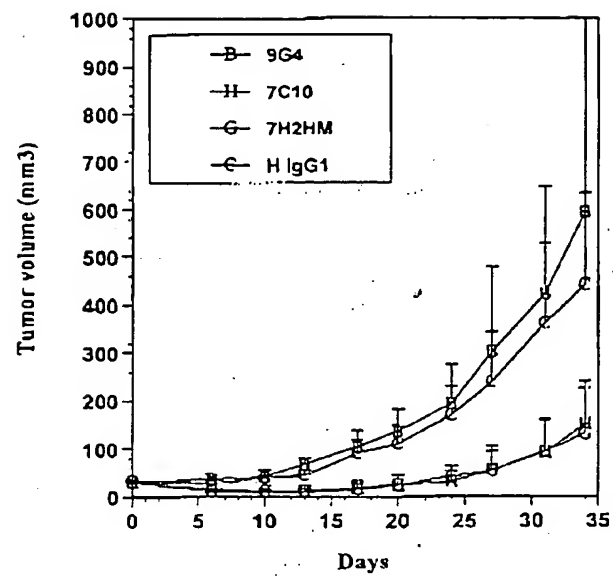


FIGURE 34A

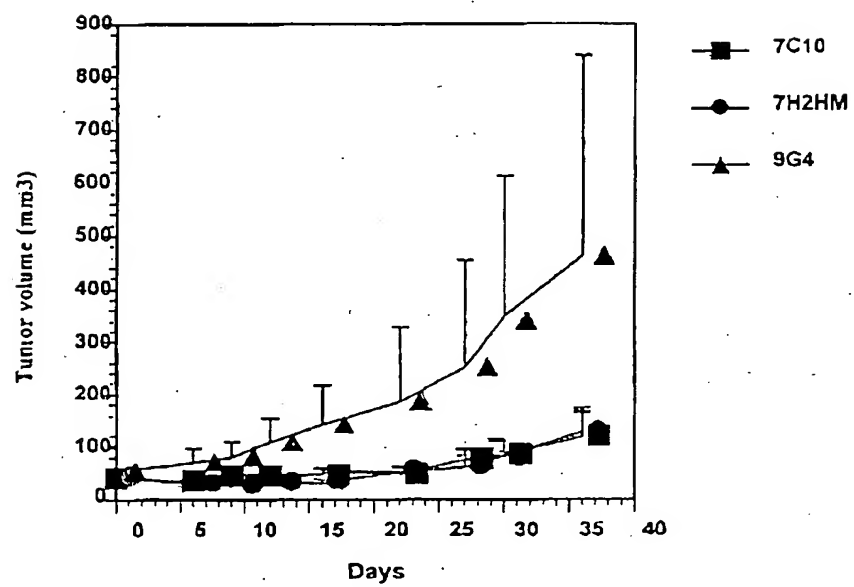


FIGURE 34B

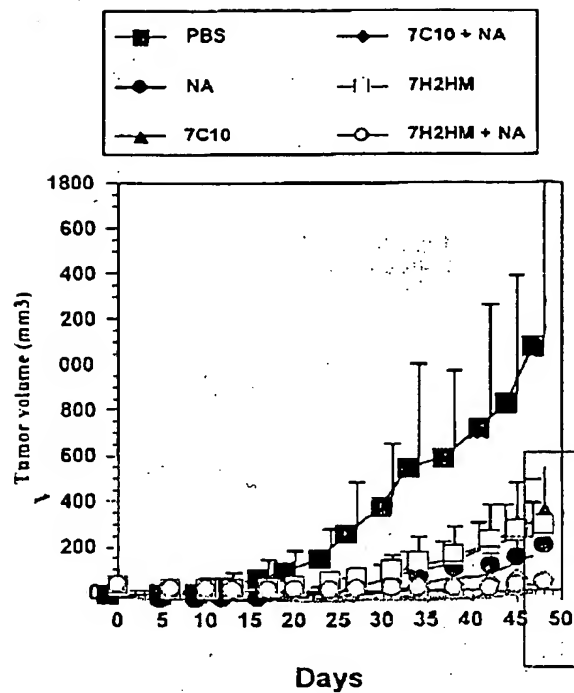


FIGURE 35A

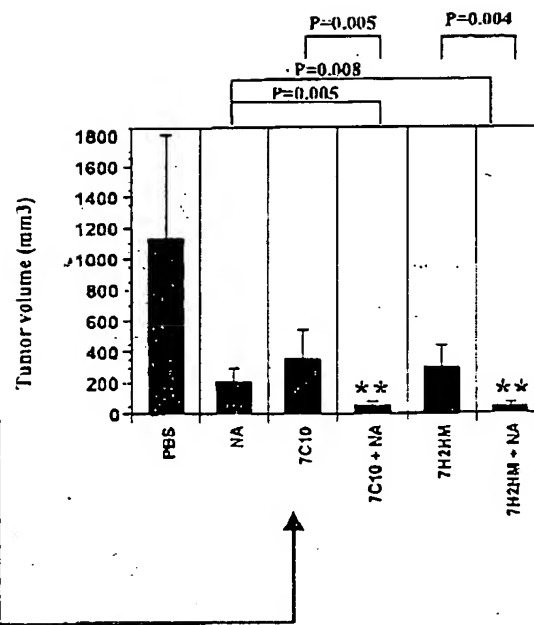


FIGURE 35B

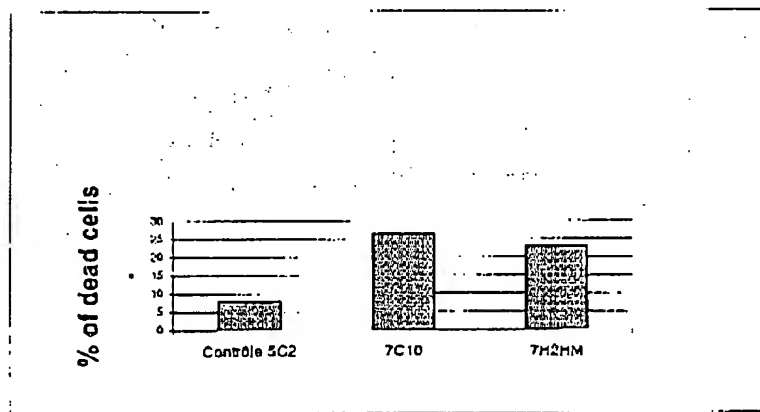


FIGURE 36

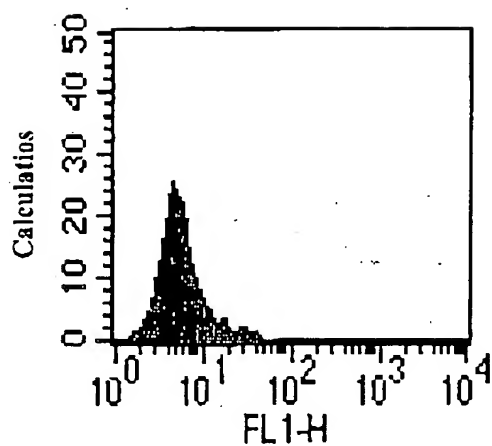


FIGURE 37A

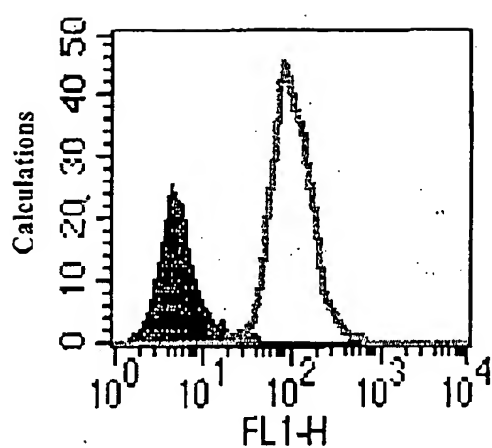


FIGURE 37B

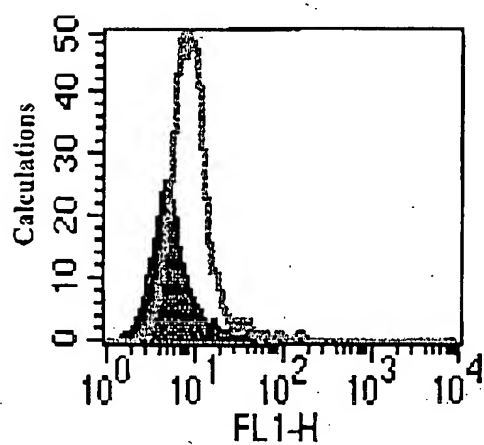


FIGURE 37C

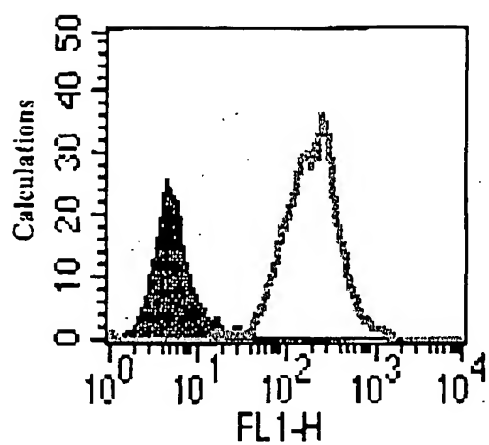


FIGURE 37D

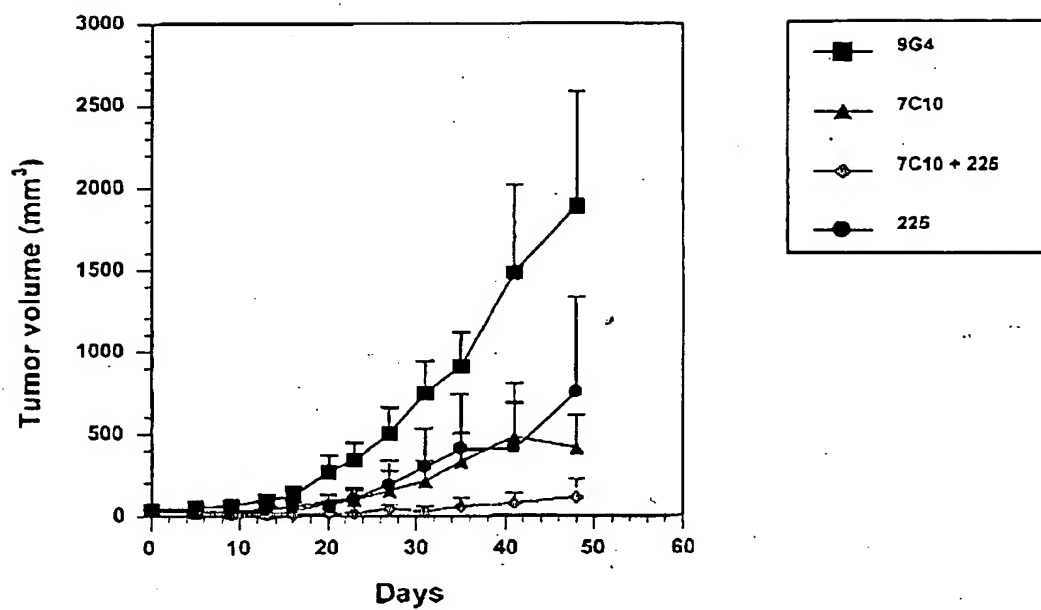


FIGURE 38

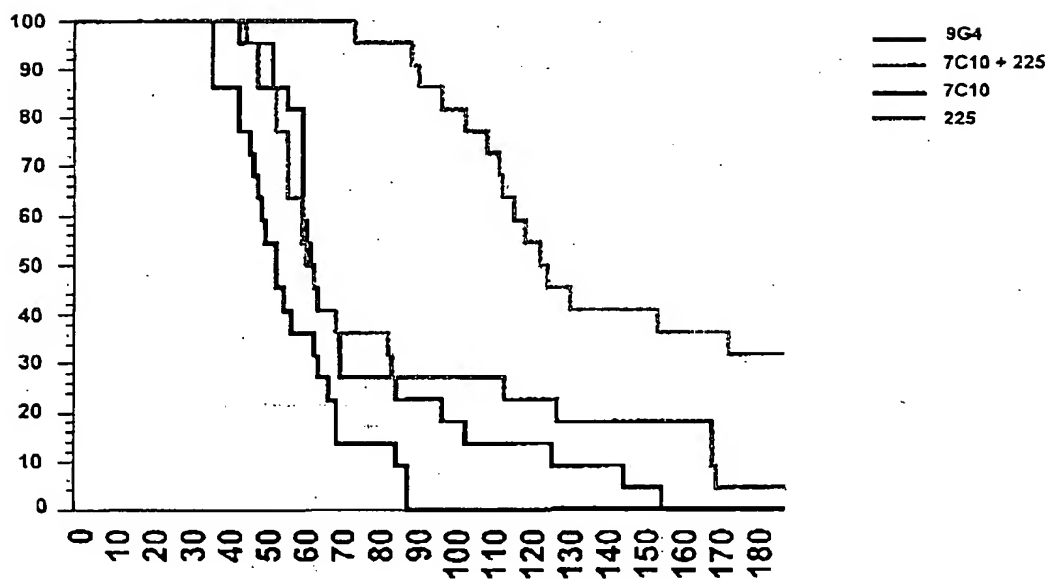


FIGURE 39

FIGURE 40A

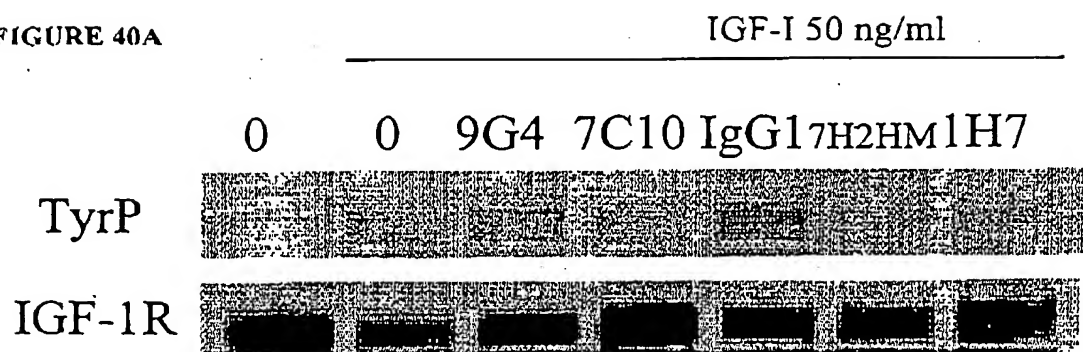


FIGURE 40B

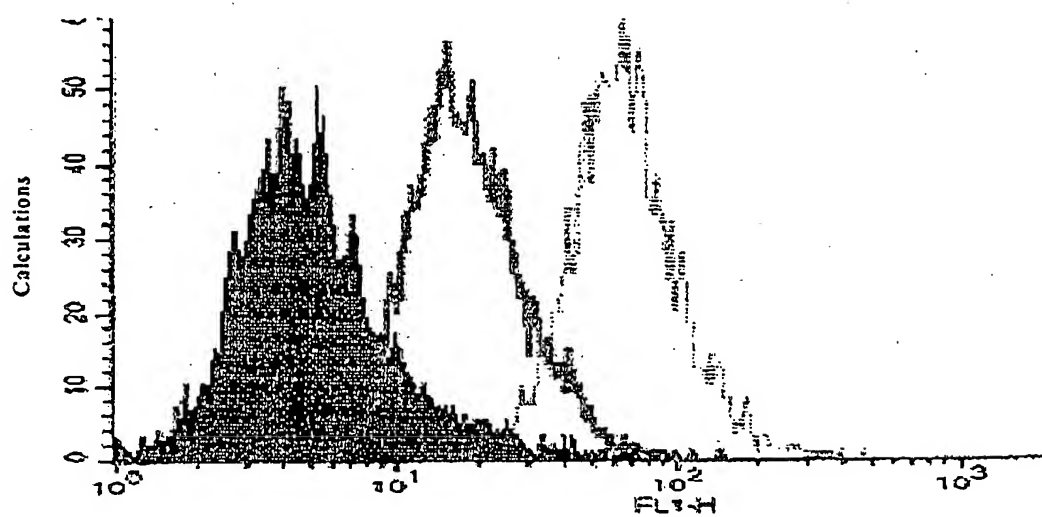
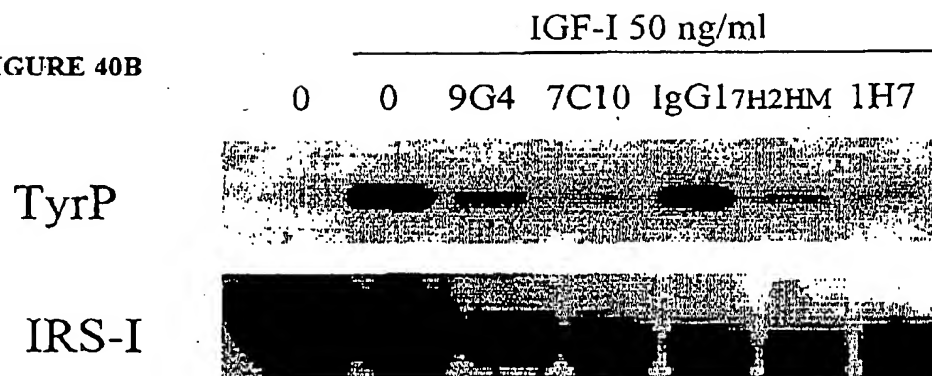


FIGURE 41

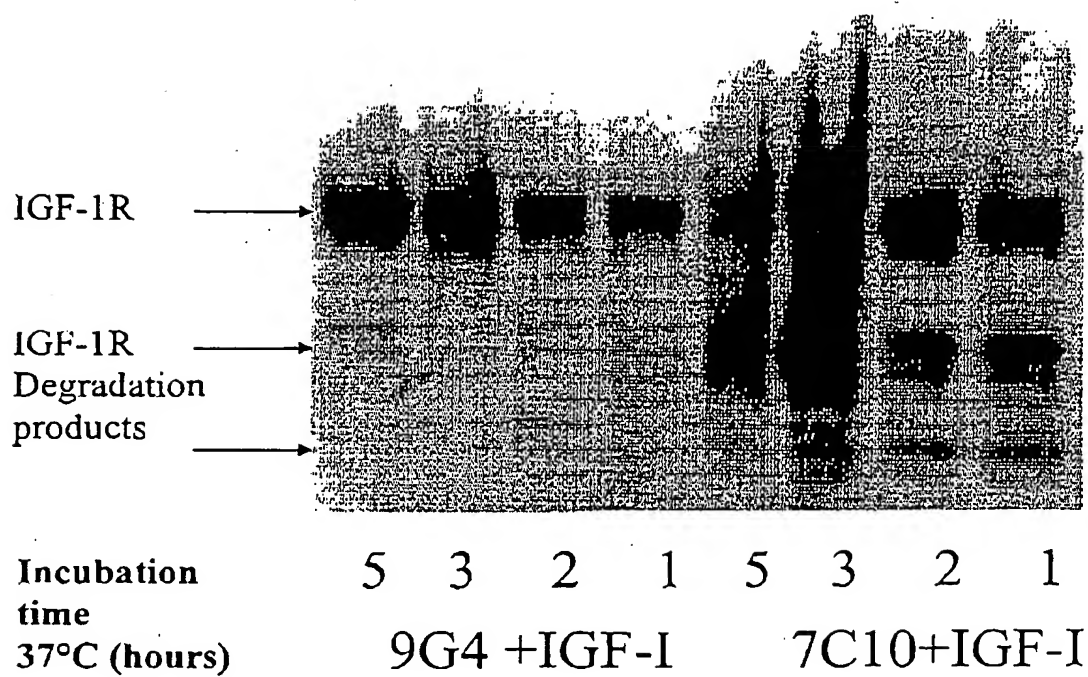


FIGURE 42A

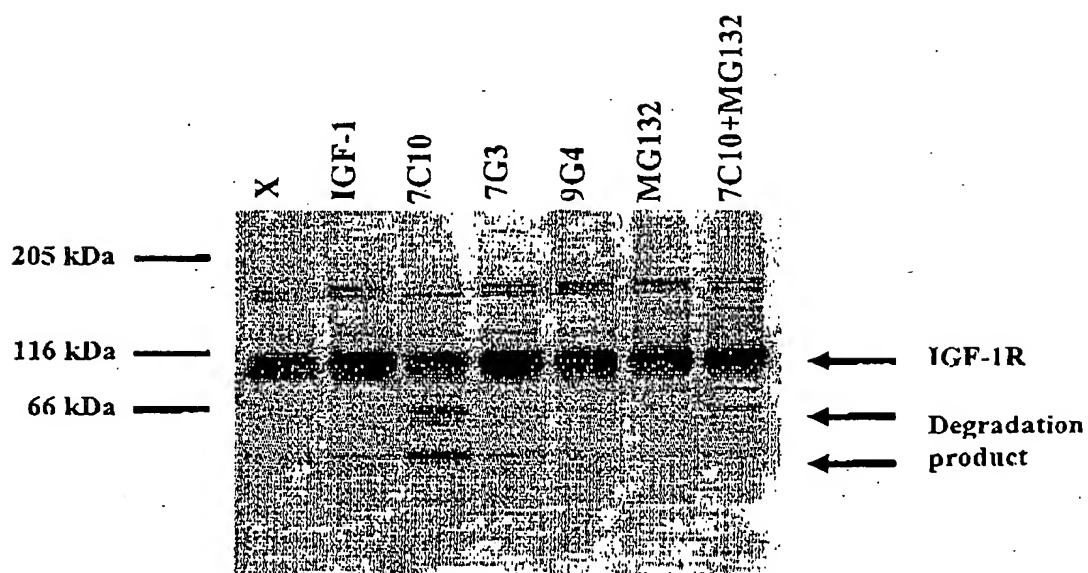


FIGURE 42B

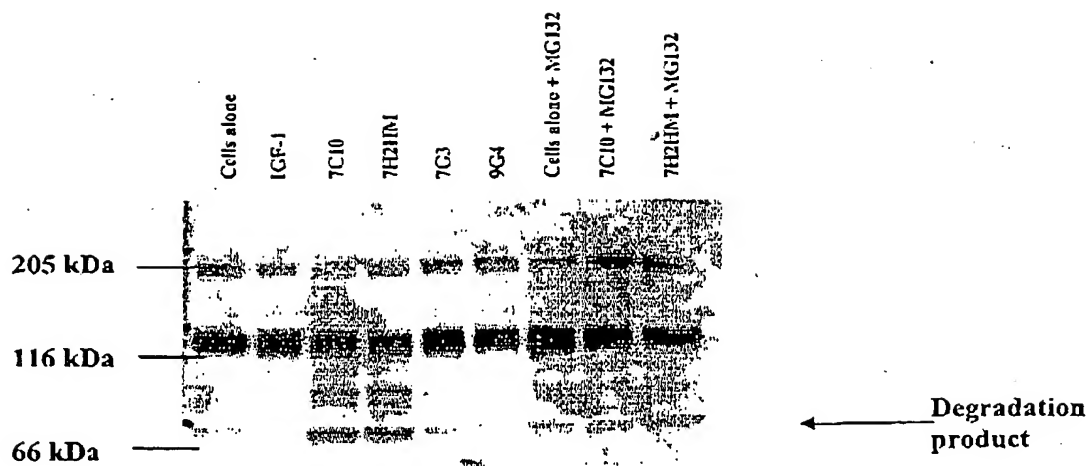


FIGURE 42C

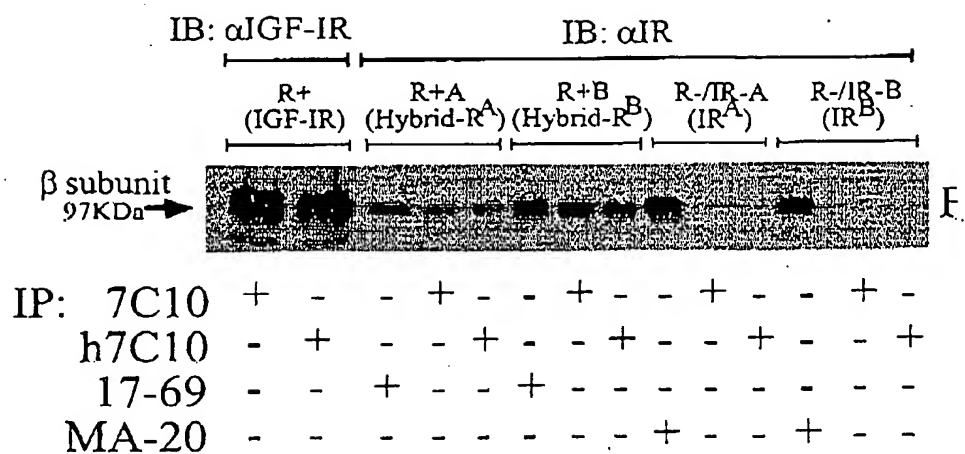


FIGURE 43A

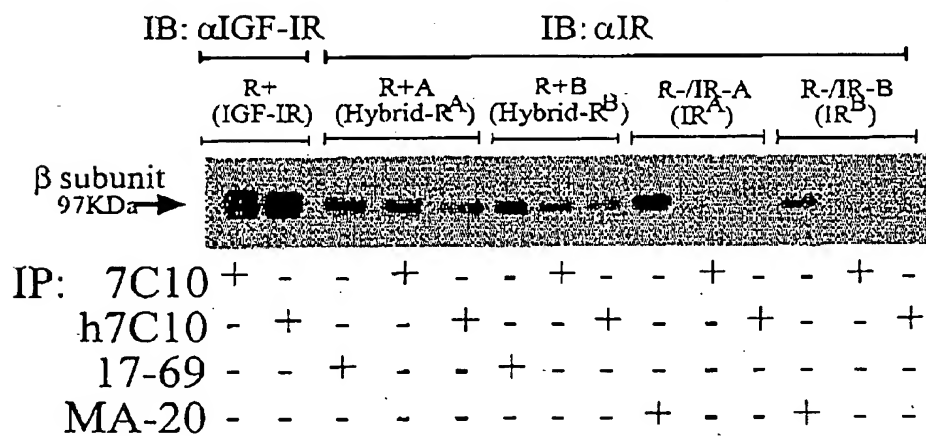


FIGURE 43B



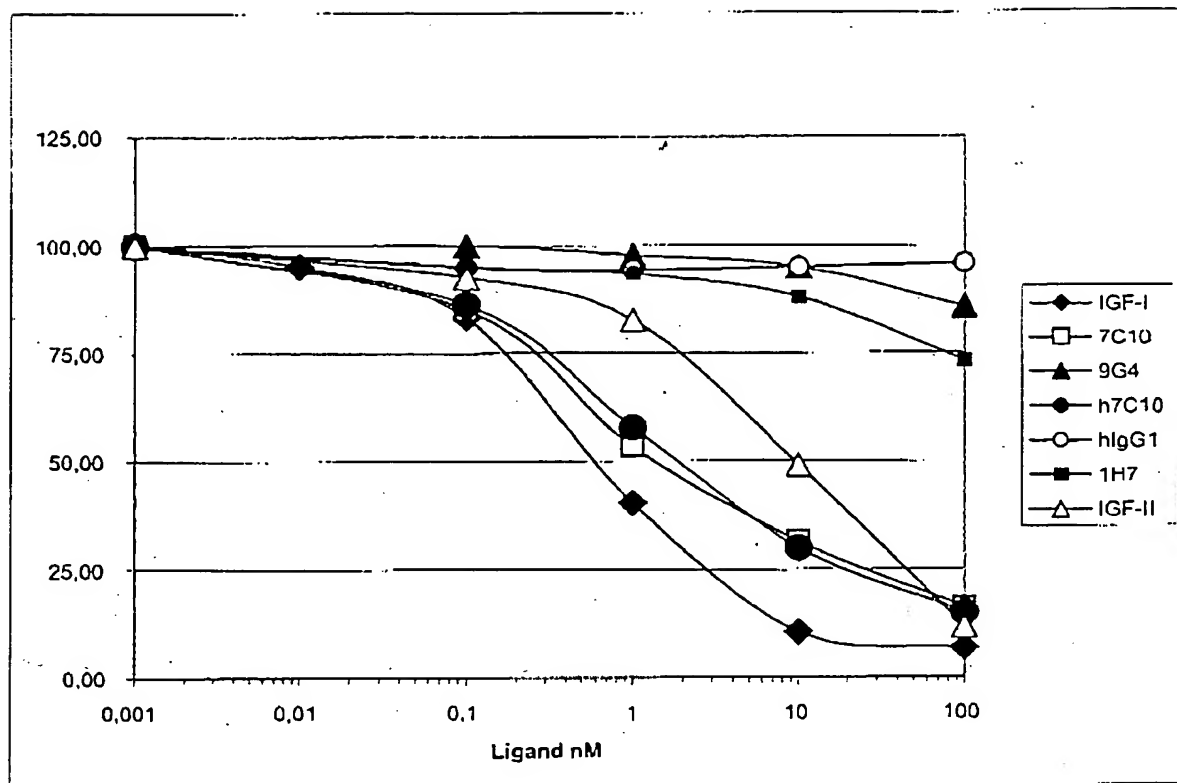


FIGURE 44

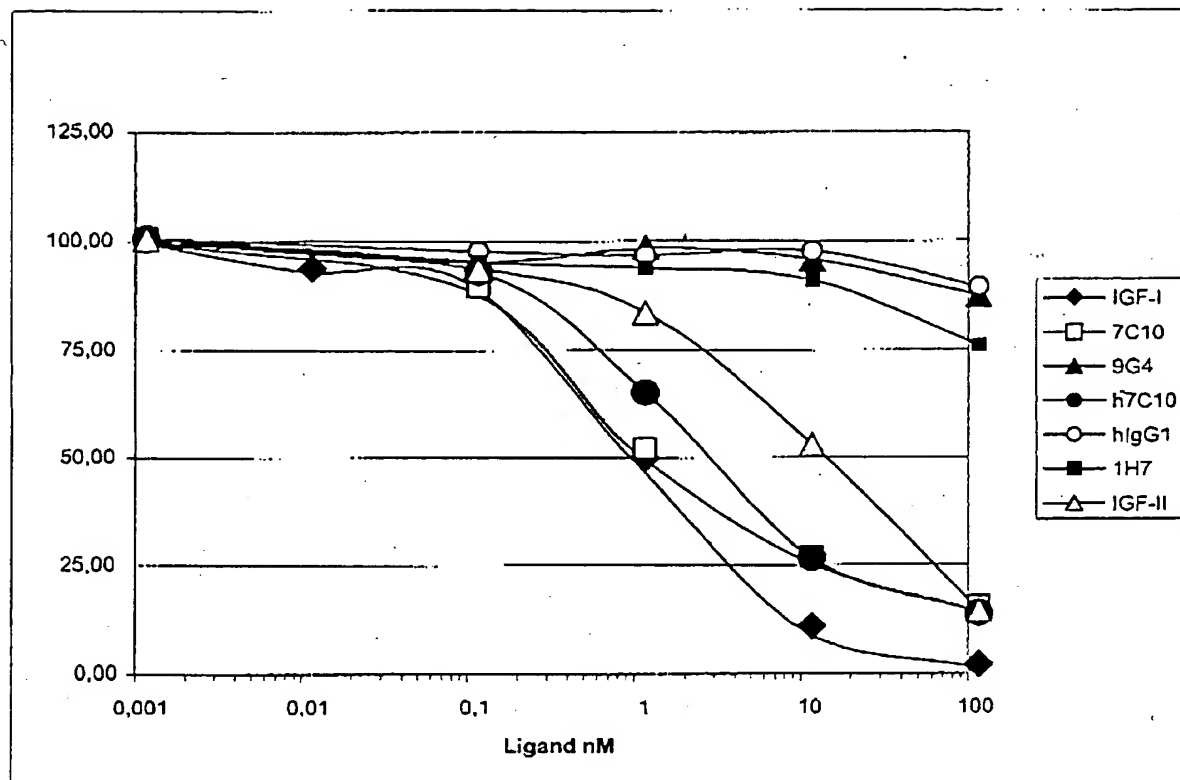


FIGURE 45

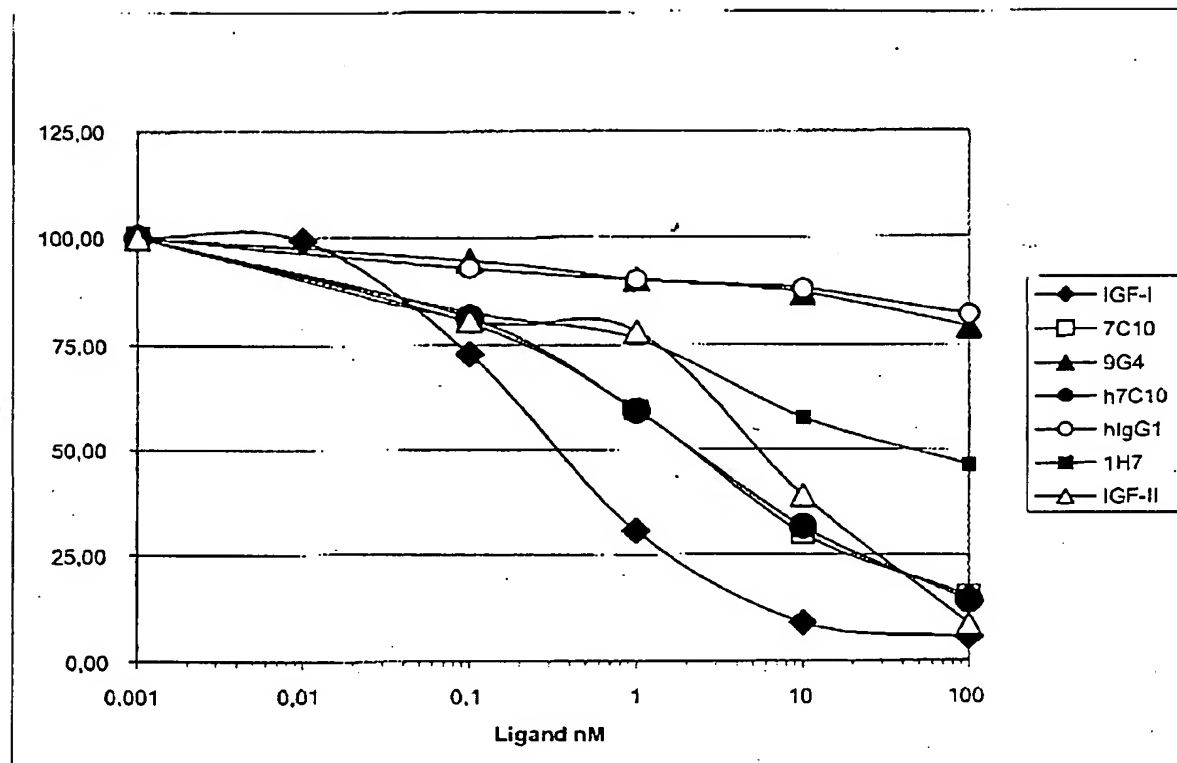


FIGURE 46

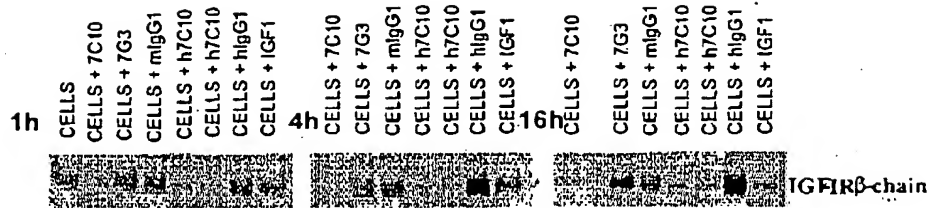


FIGURE 47A

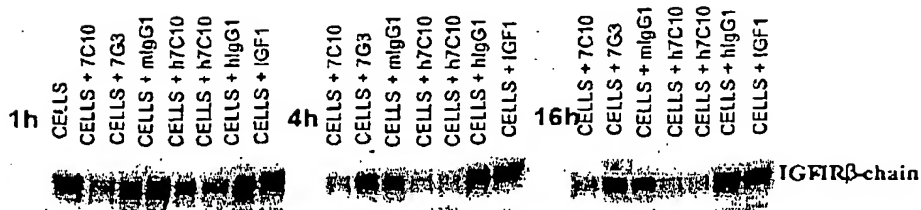


FIGURE 47B

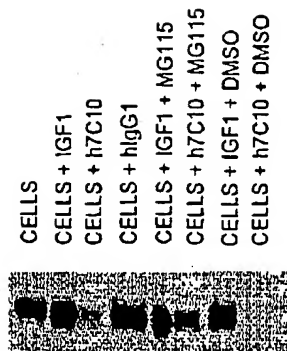


FIGURE 48

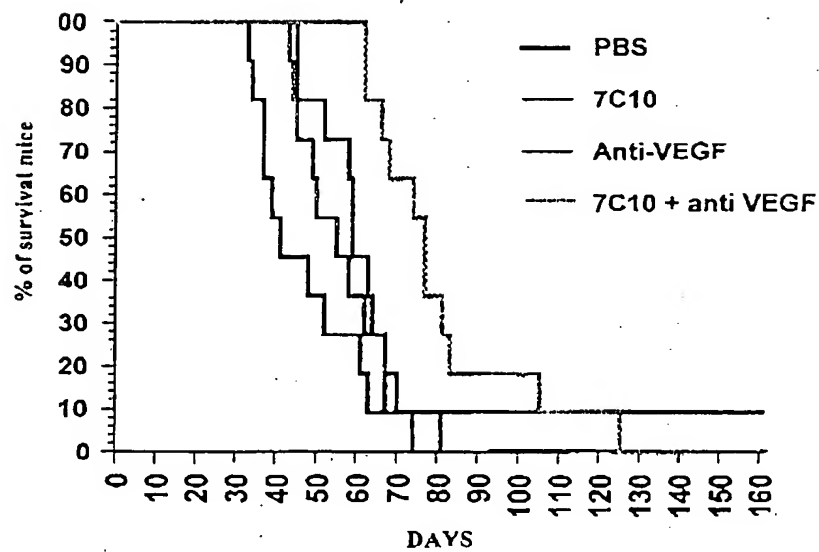


FIGURE 49

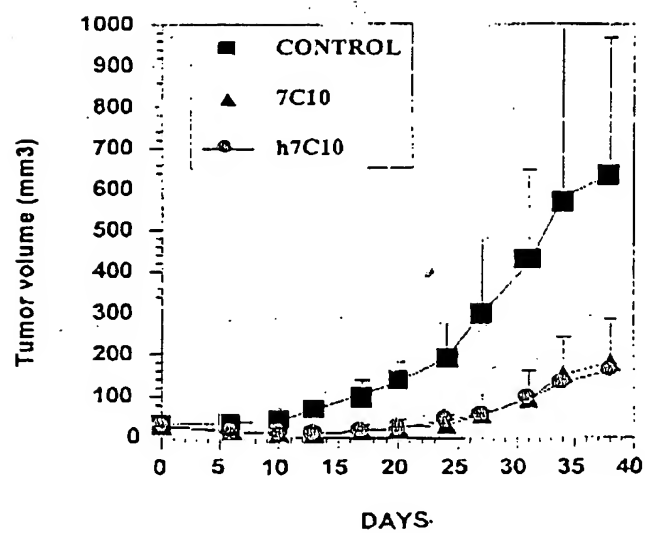


FIGURE 50

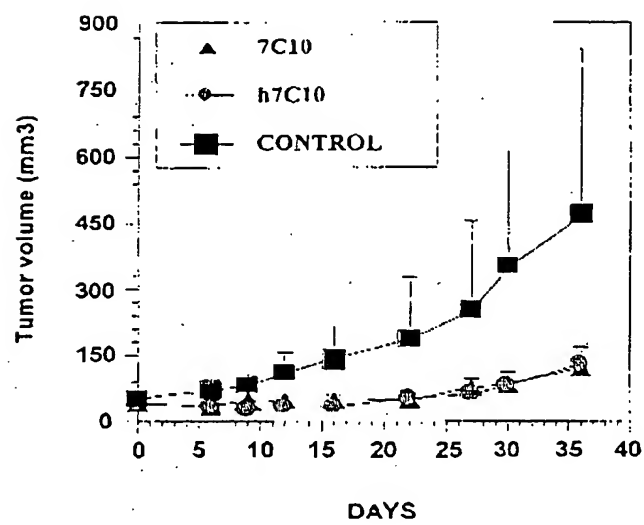


FIGURE 51

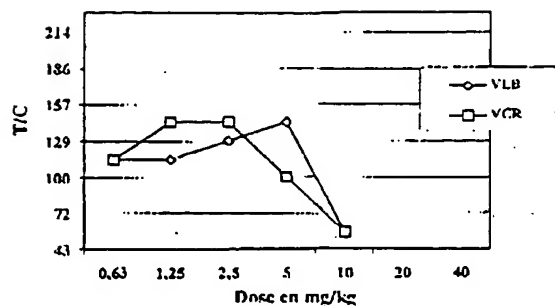


FIGURE 52

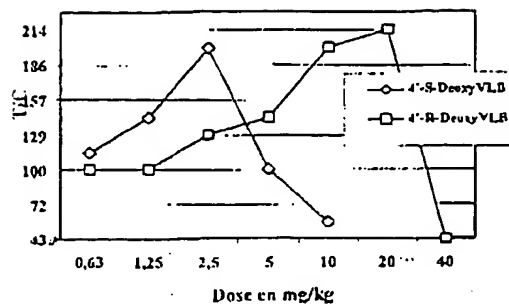


FIGURE 53

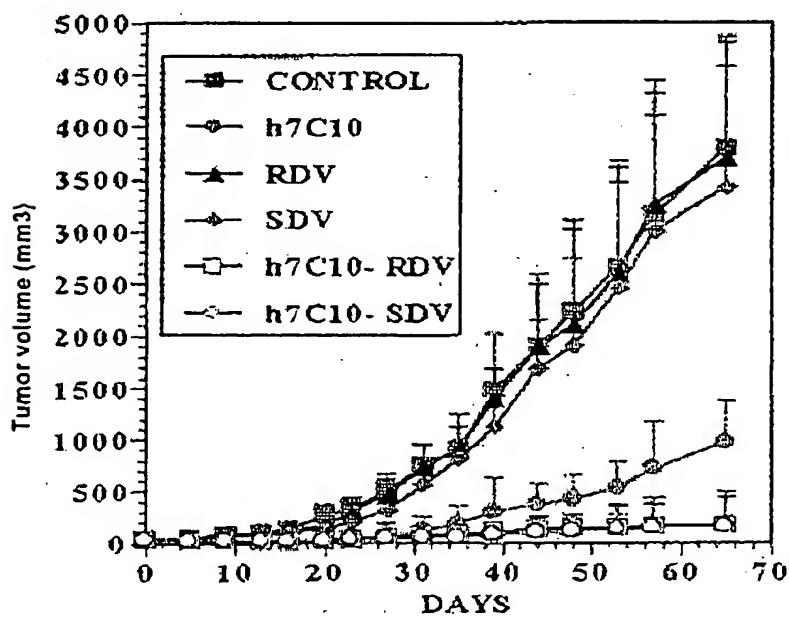


FIGURE 54